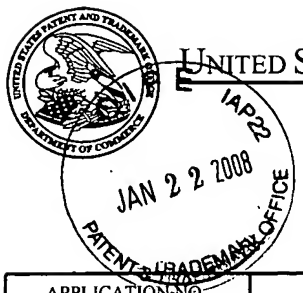
IFW



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,046	09/16/2003	Scott E. Miller	B1102.70027US00	2591

7590 01/18/2008

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EXAMINER	
BOWERS, NATHAN ANDREW	
ART UNIT	**PAPER NUMBER**
1797	

MAIL DATE	DELIVERY MODE
01/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,046	MILLER ET AL.	
	Examiner	Art Unit	
	Nathan A. Bowers	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,35,41-44,46-50,53 and 81-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,35,41-44,46-50,53 and 81-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01 November 2007 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of

the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 34, 35, 43, 44, 46, 47, 49, 50, 53, 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman (US 6653124) in view of Rao (US 20040121453).

With respect to claims 34, 35 and 44, Freeman discloses an apparatus comprising a device having a predetermined reaction site (Figure 2:12) having a volume of less than 1 milliliter. This is described in column 1, lines 41-52 and in column 23, line 61 to column 24, line 48. Although Freeman does not describe the exact volume of the reactors, Freeman does indicate in column 1, lines 23-31 and throughout the reference that microfluidic bioreactors capable of accommodating nanoliter and microliter scale quantities are well known in the art. Column 24, lines 25-28 and column 29, lines 46-50 indicate that the apparatus comprises dissolved oxygen and pH measuring devices. Freeman, however, does not expressly disclose that the oxygen and pH sensors comprise a dye, a fluorescent molecule, or a chromogenic molecule.

Rao discloses a micro scale bioreactor comprising dissolved oxygen sensors that employ ruthenium based silicone rubber sensing films. The sensing films include a dye that serves to indicate varying oxygen concentrations in the reactor. This is disclosed in paragraphs [0100]-[0108].

Freeman and Rao are analogous art because they are from the same field of endeavor regarding microfluidic bioreactors.

At the time of the invention, it would have been obvious to utilize dissolved oxygen sensors that employ a dye in the bioreactor of Freeman. In paragraphs [0104] and [0106], Rao teaches that ruthenium dyes are advantageous because they may be incorporated into films that are easily attached to the interior bioreactor wall. Ruthenium dye based sensors are also advantageous because their measurements are equilibrium based and do not consume oxygen.

With respect to claim 43, Freeman and Rao disclose the apparatus in claim 34 wherein a plurality of reactors (12) are present. This is disclosed by Freeman in Figures 1 and 2.

With respect to claims 46 and 81, Freeman and Rao disclose the apparatus in claim 34 wherein at least one surface of the predetermined reaction site comprises a polymer. Column 16, line 44 to column 17, line 30 of Freeman indicates that polymer and copolymer adhesive layers are added to the microchambers. Column 10, lines 39-50 state that the surfaces of the reaction area are coated with proteins to facilitate cell binding. Column 14, lines 20-32 state that the reaction sites are constructed from polyesters and/or polyethylenes.

With respect to claims 47 and 82, Freeman and Rao disclose the apparatus in claim 34 wherein the living cell is either a mammalian or insect cell. The apparatus of Freeman is fully capable of culturing these cell types. Throughout the reference,

Freeman describes drug testing by providing cell-based screening, so it can safely be assumed that the device is especially geared towards the culture of human tissue cells.

With respect to claims 49, 50 and 53, Freeman and Rao disclose the apparatus in as previously described above. In addition, Freeman teaches in column 29, lines 46-50 that it is known in the art to monitor temperature during cell culturing procedures.

2) Claims 34. 35. 44. 46. 47. 49. 50. 53 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheppard Jr. (US 6143247) in view of Rao (US 20040121453).

With respect to claims 34, 35 and 44, Sheppard Jr. discloses an apparatus comprising a device having a predetermined reaction site (Figure 2:24) characterized by a volume of less than 1 milliliter. This is described in column 35. line 22 to column 36. line 22. Column 15. lines 48-55 teach that the volume of the reaction site ranges from 5 to 1.000 microliters. Column 18, lines 18-30 state that the device includes various detectors, sensors, temperature control elements, and control systems. Specifically, the use of pH and dissolved gas sensors when culturing cells is considered to be well known in the art. Sheppard Jr., however, does not expressly disclose that the oxygen and pH sensors comprise a dye. a fluorescent molecule, or a chromogenic molecule.

Rao discloses a micro scale bioreactor comprising dissolved oxygen sensors that employ ruthenium based silicone rubber sensing films. The sensing films include a dye that serves to indicate varying oxygen concentrations in the reactor. This is disclosed in paragraphs [0100]-[0108].

Sheppard Jr. and Rao are analogous art because they are from the same field of endeavor regarding microfluidic bioreactors.

At the time of the invention, it would have been obvious to utilize dissolved oxygen sensors that employ a dye in the bioreactor of Sheppard Jr. In paragraphs [0104] and [0106]. Rao teaches that ruthenium dyes are advantageous because they may be incorporated into films that are easily attached to the interior bioreactor wall. Ruthenium dye based sensors are also advantageous because their measurements are equilibrium based and do not consume oxygen.

With respect to claim 46, Sheppard Jr. and Rao disclose the apparatus in claim 34 wherein at least one surface of the predetermined reaction site comprises a polymer. Column 18, lines 31-65 of Sheppard Jr. further state that the reaction area includes proteins and antibodies capable of binding to cultured cells.

With respect to claims 47 and 82, Sheppard Jr. and Rao disclose the apparatus in claim 34 wherein the living cell is either a mammalian or insect cell. Sheppard Jr. specifically discloses the use of mammalian cells in column 18, lines 31-36. the apparatus is considered fully capable of accommodating insect cells.

With respect to claims 49, 50 and 53, Sheppard Jr. and Rao disclose the apparatus in as previously described above. In addition, Sheppard Jr. teaches in column 25, lines 37-67 that it is known in the art to monitor temperature during cell culturing procedures.

3) Claims 41, 42 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Freeman (US 6653124) or Sheppard Jr. (US 6143247) in view of Rao (US 20040121453) each as applied to claim 34, and further in view of Kapur (US 6548263).

Freeman/Sheppard Jr. and Rao disclose the apparatus set forth in claim 34 as set forth in the 35 U.S.C. 103 rejections above. Both the Freeman and Sheppard Jr. references teach the use of sensors and detectors, and therefore imply that a control system is utilized for regulating system parameters. Freeman and Sheppard Jr., however, do not expressly disclose the use of a processor for managing data obtained by the sensors.

Kapur discloses a microfluidic substrate for culturing and screening cells. Column 7, lines 63-67, column 26, lines 1-5, and column 39, line 60 to column 40, line 25 state that a controller, sensors, and associated actuators are provided for regulating temperature, oxygen content, and carbon dioxide content during cellular growth.

Freeman, Sheppard Jr., Rao and Kapur are analogous art because they are from the same field of endeavor regarding microfluidic cell culture systems.

At the time of the invention, it would have been obvious to ensure that the microfermenters of Freeman and Sheppard Jr. were in communication with control systems capable of regulating dissolved oxygen content, pH, and temperature. Freeman and Sheppard Jr. both indicate that the use of sensors capable of determining various environmental factors is well known in the bioreactor art. By providing an linked control system, one would have been able to monitor and manage the bioreactor automatically, and thereby increase the efficiency of the operation.

4) Claims 83, 84, 87-91 and 93-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freeman (US 6653124) in view of Rao (US 20040121453) and Barbera-Guillem (US 6455310).

With respect to claims 83, 84, 88, 95 and 96, Freeman and Rao disclose the apparatus set forth in the 35 U.S.C. 103 rejections above. Rao discloses the use of a fluorescent molecule, rather than chromogenic molecules, to detect the presence of oxygen in a culture medium.

Barbera-Guillem discloses a cell culture apparatus comprising a chamber (Figure 9:40) for growing cells. Barbera-Guillem teaches in column 10, lines 14-28 that chromogenic molecules are added to the chamber, and are capable of inducing a color change in response to an environmental factor. Barbera-Guillem teaches that detection of the color change is an easy way to recognize changes to various factors (such as pH) within the sample solution.

Freeman, Rao and Barbera-Guillem are analogous art because they are from the same field of endeavor regarding microfluidic bioreactors.

At the time of the invention, it would have been obvious to add a detection mechanism based on the presence of a chromogenic molecule to the fluorescence detection system disclosed by Freeman and Rao. In column 10, lines 14-28, Barbera-Guillem teaches that chromogenic detection systems are well known in the art, and are beneficial because they produce a color change that can be detected either by eye or by using a photodetector.

With respect to claim 87, Freeman, Rao and Barbera-Guillem disclose the apparatus in claim 83 wherein a plurality of reactors (12) are present. This is disclosed by Freeman in Figures 1 and 2.

With respect to claims 89 and 90, Freeman, Rao and Barbera-Guillem disclose the apparatus in claim 83 wherein at least one surface of the predetermined reaction site comprises a polymer. Column 16, line 44 to column 17, line 30 of Freeman indicates that polymer and copolymer adhesive layers are added to the microchambers. Column 10, lines 39-50 state that the surfaces of the reaction area are coated with proteins to facilitate cell binding. Column 14, lines 20-32 state that the reaction sites are constructed from polyesters and/or polyethylenes.

With respect to claims 91 and 94, Freeman, Rao and Barbera-Guillem disclose the apparatus in claim 83 wherein the living cell is either a mammalian or insect cell. The apparatus of Freeman is fully capable of culturing these cell types. Throughout the reference, Freeman describes drug testing by providing cell-based screening, so it can safely be assumed that the device is especially geared towards the culture of human tissue cells.

With respect to claim 93, Freeman and Rao disclose the apparatus in claim 83. In addition, Freeman teaches in column 29, lines 46-50 that it is known in the art to monitor temperature during cell culturing procedures.

5) Claims 83, 84, 88, 89, 91, 93-96are rejected under 35 U.S.C. 103(a) as being unpatentable over Sheppard Jr. (US 6143247) in view of Rao (US 20040121453) and Barbera-Guillem (US 6455310).

With respect to claims 83, 84, 88, 95 and 96, Sheppard Jr. and Rao disclose the apparatus set forth in the 35 U.S.C. 103 rejections above. Rao discloses the use of a fluorescent molecule, rather than chromogenic molecules, to detect the presence of oxygen in a culture medium.

Barbera-Guillem discloses a cell culture apparatus comprising a chamber (Figure 9:40) for growing cells. Barbera-Guillem teaches in column 10, lines 14-28 that chromogenic molecules are added to the chamber, and are capable of inducing a color change in response to an environmental factor. Barbera-Guillem teaches that detection of the color change is an easy way to recognize changes to various factors (such as pH) within the sample solution.

Sheppard Jr., Rao and Barbera-Guillem are analogous art because they are from the same field of endeavor regarding microfluidic bioreactors.

At the time of the invention, it would have been obvious to add a detection mechanism based on the presence of a chromogenic molecule to the fluorescence detection system disclosed by Sheppard Jr. and Rao. In column 10, lines 14-28, Barbera-Guillem teaches that chromogenic detection systems are well known in the art, and are beneficial because they produce a color change that can be detected either by eye or by using a photodetector.

With respect to claim 89, Sheppard Jr., Rao and Barbera-Guillem disclose the apparatus in claim 46 wherein at least one surface of the predetermined reaction site comprises a polymer. Column 18. lines 31-65 of Sheppard Jr. further state that the reaction area includes proteins and antibodies capable of binding to cultured cells.

With respect to claims 91 and 94, Sheppard Jr., Rao and Barbera-Guillem disclose the apparatus in claim 34 wherein the living cell is either a mammalian or insect cell. Sheppard Jr. specifically discloses the use of mammalian cells in column 18, lines 31-36. the apparatus is considered fully capable of accommodating insect cells.

With respect to claim 93, Sheppard Jr. and Rao disclose the apparatus in claim 83. In addition, Sheppard Jr. teaches in column 25, lines 37-67 that it is known in the art to monitor temperature during cell culturing procedures.

6) Claims 85. 86 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Freeman (US 6653124) or Sheppard Jr. (US 6143247) in view of Rao (US 20040121453) and Barbera-Guillem (US 6455310) each as applied to claim 34, and further in view of Kapur (US 6548263).

Freeman/Sheppard Jr., Rao and Barbera-Guillem disclose the apparatus set forth in claim 34 as set forth in the 35 U.S.C. 103 rejections above. Both the Freeman and Sheppard Jr. references teach the use of sensors and detectors, and therefore imply that a control system is utilized for regulating system parameters. Freeman and Sheppard Jr.,

however, do not expressly disclose the use of a processor for managing data obtained by the sensors.

Kapur discloses a microfluidic substrate for culturing and screening cells. Column 7, lines 63-67, column 26, lines 1-5, and column 39, line 60 to column 40, line 25 state that a controller, sensors, and associated actuators are provided for regulating temperature, oxygen content, and carbon dioxide content during cellular growth.

Freeman, Sheppard Jr., Rao, Barbera-Guillem and Kapur are analogous art because they are from the same field of endeavor regarding microfluidic cell culture systems.

At the time of the invention, it would have been obvious to ensure that the microfermenters of Freeman and Sheppard Jr. were in communication with control systems capable of regulating dissolved oxygen content, pH, and temperature. Freeman and Sheppard Jr. both indicate that the use of sensors capable of determining various environmental factors is well known in the bioreactor art. By providing an linked control system, one would have been able to monitor and manage the bioreactor automatically, and thereby increase the efficiency of the operation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d

2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34, 35, 43, 44, 49, 50, 53, 83, 84, 87, 88, 93, 95 and 96 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 120, 130, 132, 141 and 157-159 of copending Application No. 10/664067.

The claims of copending Application No. 10/664067 disclose an apparatus comprising a reaction site having a volume of less than 500 microliters. The claims further describe the use of temperature, pH, glucose, pressure, and optical density sensors. The instant application is generic to copending Application No. 10/664067 because copending Application No. 10/664067 discloses additional features such as a membrane dividing the reaction site.

This is a provisional obviousness-type double patenting rejection.

Response to Arguments

Applicant's arguments filed 01 November 2007 with regard to the 35 U.S.C. 103 rejections involving the combination of Freeman and Rao and the combination of Sheppard Jr. and Rao have been fully considered but they are not persuasive.

Applicant's principle arguments are

(a) Rao only discloses the use of a dye, and does not disclose the use of a fluorescent molecule.

In response to Applicant's arguments, please consider the following comments.

The dyes disclosed by Rao are fluorescent molecules. Paragraphs [0104]-[0108] disclose a number of fluorescent ruthenium and porphyrin dyes that are used during oxygen detection. The fluorescent dyes of Rao are a specific type of fluorescent molecule capable of working with a sensor to determine an environmental factor associated with a predetermined reaction site.

Please consider new rejections made regarding the combination of Freeman, Rao and Barbera-Guillem and the combination of Sheppard Jr., Rao and Barbera-Guillem.

The double patenting rejections over Application No. 10/664067 have been amended to now recite claims that have been newly added to the 10/664067 application.

In response to Applicant's amendments and remarks, the double patenting rejections over Application No. 10/927789 have been withdrawn.

Conclusion

This is a non-final rejection.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan A. Bowers whose telephone number is (571) 272-8613. The examiner can normally be reached on Monday-Friday 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gladys Corcoran can be reached on (571) 272-1214. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NAB

GLADYS JP CORCORAN
SUPERVISORY PATENT EXAMINER

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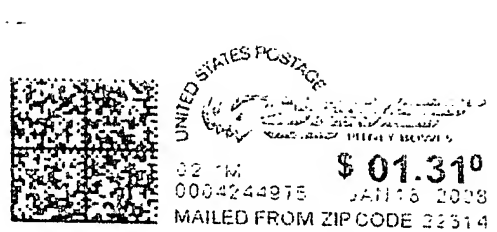

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